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Meeting Report

Innovative partnerships for medicines research: How is the landscape evolving? Highlights from the Society for Medicines Research Symposium

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Summary

The discovery and development of new drugs to treat many of society's most complex and inadequately treated diseases remains a lengthy, high-risk and high-cost endeavor. R&D costs continue to increase, while the number of new drug launches is failing to improve. This is prompting many in the research community to question the long-term viability of current drug discovery and development models. The last decade has seen a dramatic increase in the number of new institutes being established that aim to improve the efficiency and success rates of drug discovery and development, by deploying innovative new business models. Central to the mission of these organizations is to identify improved routes for translation of novel preclinical research findings into more successful clinical outcomes. A panel of experts from academia, industry and charities shared their views on how these institutes have developed and discussed how successful they have been in addressing some of these challenges. The many innovative new models of drug discovery and development, together with some of the experiences, lessons learned and future strategies were also highlighted. This Society for Medicines Research symposium was held at the Babraham Research Campus, Cambridge, and hosted by MedImmune.

Key words: Drug development – Drug discovery – Partnerships

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AstraZeneca Open Innovation Drug Discovery

Dr. Dave Smith from AstraZeneca (AZ) gave the first presentation of the meeting titled, "AstraZeneca Open Innovation Drug Discovery". Dr. Smith highlighted that Open Innovation initiatives have been favored by many companies with AZ being no exception. AZ started its Open Innovation projects in 2011. AZ works with a comprehensive suite of partnership models where the company shares chemical tools to help validate new targets (Target Innovation) and to open up new clinical opportunities for existing compounds (clinical compound bank).

AZ currently has over 50 collaborative projects directed towards new targets distributed predominantly in the E.U. and U.S. but also in Asia and Australia. These projects tend to be focused towards AZ therapy areas.

The Target Innovation concept is aimed at screening novel targets to produce tool compounds for target validation and lead compound series for drug discovery. The screening can be high-throughput diversity screens, phenotypic screens

or fragment screens. Specific examples of strategic partnerships include those with LifeArc and Sussex University. The MRC Technology (MRCT) partnership is in the fifth year with 9 projects competed or currently ongoing. When the partnership started it was disease/target agnostic but now it is focused on the epigenetics of respiratory disease. MRCT brings expertise on targets and drug discovery and AZ brings expertise on screening compounds and disease area drug discovery expertise. With Sussex University, AZ has a 4-year multitarget collaboration. This includes GBP 6M funding from the Wellcome Trust. The collaboration utilizes Sussex deep expertise in DNA Damage Response coupled with AZ's Hit Identification Capabilities.

AZ has established the UK Centre for Lead Discovery based within their research facility in Alderley Park but soon to be transferred to Cambridge. Current partners engaged with the center include Cancer Research UK (CRUK) and the Medical Research Council (MRC). The center contains infrastructure for lead discovery by high-throughput screening of the AZ compound collection, with AZ scientists engaged in AZ projects, but working side by side with academic scientists engaged in academic projects.

AZ has established a quid pro quo exchange of compounds with other companies with no requirement for cash payments or royalties. The arrangement allows organizations to securely share large sets of compounds in order to increase the chance of finding hits. The key challenges that have been identified with sharing compound collections include securing stakeholder support, demonstrating additional value from partner collections and ensuring core AZ assets are protected.

Dr. Smith outlined several challenges for Open Innovation, namely contracting can be slow even with standard agreements. In addition, resourcing and funding gaps for some academic projects and balancing innovation with disease area alignment and likelihood of success.

Potential future areas for Open Innovation to develop across the industry were discussed, e.g., sharing of safety data, development data, project data and different types of libraries such as antibodies, siRNA and CRISPR.

LAB282 Spearheads Evotec's Academic BRIDGE Concept

In the second presentation of the day, Dr. Thomas Hanke highlighted that one of the issues faced by large pharmaceutical companies is cost pressure. Internal research is cost-intensive and the costs are fixed. However, partnerships between academia and industry provide more cost flexibility.

Dr. Hanke described how a novel risk sharing partnership has recently been established in Oxford which utilizes the strengths of academia, pharma/biotech and commercial financing partners in order to improve the quality and speed of innovation in validating preclinical concepts. Termed LAB282, the partnership was initiated in November 2016 by Oxford University, Oxford University Science (the University's research commercialization company), Oxford Science Innovation (an organization that leads a GBP 13 million investment fund) and Evotec (the industrial partner that aims to BRIDGE the transition of novel ideas through to preclinical validation of therapeutic concepts). A clear framework for collaboration is established which includes pre-negotiated agreements with all parties. This allows for transparent rules for distribution of revenues between all parties that provide IP, infrastructure, specific know-how and/or funding.

One of the key features of the BRIDGE concept is that a resident industrial expert is embedded in the Oxford eco system. This has the advantage of quick initial discussions with principal investigators in order to assess the initial concept and to provide local advice in order to prepare seed fundable project plans. In addition, access to assays and expertise for validation of preclinical concepts can be provided through a single experienced industrial partner. The overall aim is to maximize identification of new projects, reduce contract agreement timelines and provide validation of technology and key concepts. The LAB282 BRIDGE concept aims to speed up the process from concept to formation of a new company or partnerable asset by half, from the traditional timeline of 3 years to closer to 1.5 years.

Dr. Hanke described the qualities a current project adopted by LAB282 has ("Bugs to Drugs"). In particular, it has a novel therapeutic approach, a unique insight into disease biology, a well-defined indication with a high unmet need, a clear therapeutic format, a promising IP position and qualified team with entrepreneurial ambition.

While the BRIDGE concept is being trialed in Oxford, it is suitable for partners from other academic institutes, capital providers and pharma.

The Crick Innovative Model for Translation – Early Signs of Success?

Dr. Veronique Birault, Head of Translation at The Francis Crick Institute (Crick), gave an excellent overview of the rationale behind the partnership that led to it being established, while covering its capabilities, strategy, goals and partnership models. The Crick was formed as part of a landmark partnership between the U.K.'s three largest funders of biomedical research (MRC, CRUK and the Wellcome Trust), as well as three of its leading universities (University College London, Imperial College and King's College London). It was officially opened in November 2016, will be home to around 1,350 scientists and technical staff consisting of up to 120 research groups, and has a vision based on five key "pillars":

- Pursue discovery without boundaries;
- Create future science leaders;
- Collaborate creatively to advance U.K. science and innovation;
- Accelerate translation for health and wealth;
- Engage and inspire the public.

The Crick has a broad scientific remit with very little off limit and aims to discover the biology underlying human health, improving the treatment, diagnosis, and prevention of human disease. Research teams are kept deliberately small, with no departments or divisions to foster collaboration between groups with diverse expertise including biology, physics, computing, mathematics and clinical sciences. Each research group has 6 years of core funding provided by the Crick, can be renewed for another 6 years but then must relocate thereby distributing experience gained to other institutions. Researchers are supported by 14 core science technology platforms, ranging from cutting edge mass spectrometry, advanced sequencing to microscopy and structural biology.

The Crick's translation strategy focuses on maximizing the impact that can be generated from discovery science, measured in terms of improvements in the lives of people in the U.K. and internationally, and in new economic opportunities. The Crick approach to translation has two guiding principles:

1. "Close distance translation": The translation team and the wider embedded translation experts (applied scientists from industry, entrepreneurs in residence and clinicians) work closely with each researcher under a precompetitive framework. This 'close distance' translation improves the probability that basic science can be developed as translatable projects that can be further progressed to benefit health.
2. "Accelerate into capable hands": Focusing on accelerating ideas to the point at which it becomes an adoptable proposition, underpinned by world-class science. Accelerating the translation of projects requires an evident route to exploitation. These are developed to the point where they are suitable for adoption and investment through interactions with capable hands, i.e., industry or NHS clinicians.

An example of "close distance translation" in the early-stage, precompetitive space is that of the Crick and GlaxoSmithKline (GSK) LinkLabs Project Space. This partnership has been set up to bring the science, disease expertise and disease projects from the Crick with drug discovery expertise/platforms, compounds, reagents and biopharmaceuticals from GSK. The aim is to build shared outputs including disease knowledge, drug discovery projects, shared learning and joint publications to accelerate translational research. As of March 2017, 16 projects had been established under this collaboration, within disease areas such as cancer, tuberculosis, skin disorders and malaria. The Crick has also recently established an open science research agreement with AstraZeneca which will see researchers from AstraZeneca and the Crick collaborate on early-stage research, aiming to develop new treatments and health innovations over a 5-year period.

The Crick has also established an "Idea to Innovation" initiative that provides funding to support early-stage translational projects with the goal of providing confidence in an underlying concept, to justify continued development, funded by larger grants or philanthropy. Twelve of these projects have been supported to date, including one being led by Dr. Lucy Collinsom developing miniature light microscopes ('miniLMs') that can be used within the Correlative Light and Electron Microscopy workflow to locate and track the fluorescent cells of interest within bulk samples.

The Crick also has access to a wide network of external expertise that can be tapped to help accelerate curiosity drive science toward clinical study. Data generated by Dr. Ilaria Malanchi showing that neutrophils support lung colonization of metastasis-initiating breast cancer cells (1), was discussed with the Cancer Research UK Centre for Drug Development. Based on this discussion, appropriate expertise was found to help develop a clinical trial design to translate Dr. Malanchi's discovery.

The final way in which the Crick accelerates translation is to create spin-out companies based on research performed at the institute, and to link SMEs and biotechnology companies to harness knowledge, resources and technologies. Two spin-outs have been formed from the Crick to date:

- Achilles Therapeutics (Professor Charlie Swanton): Aims to develop and exploit T-cell immunotherapies for the treatment of cancer.
- Gamma Delta Therapeutics (Professor Adrian Hayday): Seeks to advance a novel approach to immunotherapy for the treatment of cancer and inflammatory diseases.

By using the various collaborative models described above, the Crick is closing the distance between multidisciplinary scientists and industrial partners, to accelerate translation of curiosity science toward patient benefit, with some early signs of success beginning to emerge.

The CRUK–MedImmune Alliance – a Unique Academia–Industry Partnership which will Benefit Cancer Patients

Dr. Maria Groves (Head of the CRUK–MedImmune Alliance Laboratory) gave a passionate presentation on the drivers behind establishing the CRUK–MedImmune Alliance Laboratory (CMAL), how it operates and what makes it such a unique academic–industry partnership.

CRUK has an ambition of accelerating progress to see three-quarters of people with cancer surviving the disease by 2034. To help achieve this, they have prioritized the acceleration of therapeutic discovery and increased support for collaborative approaches in this area. A key strategic decision was taken by CRUK in 2014 to further increase investment in biological therapeutics research, and an opportunity to set up and run a world-class antibody discovery laboratory in partnership with MedImmune, the global biologics R&D arm of AZ, was viewed as a route to realizing this ambition.

MedImmune has a strong track record and in-depth knowledge of biologics discovery, with over 20 years of experience developing phage display antibody libraries that have around 100 billion antibodies. Using this technology, coupled to a network of principal investigators (PIs) established by CRUK over many decades, presented an unmissable opportunity to find exclusive and novel antibody cancer targets.

The different capabilities and resources provided by each of the partners to the CMAL (see Table I below) is anticipated to produce synergies that will lead to the expedited delivery of first-in-class innovative oncology drugs, tool antibodies and reagents to advance oncology research. The CMAL was established in Cambridge and officially opened in September 2015 with the vision of establishing "collaborative novel antibody discovery for the benefit of cancer patients."

In this joint laboratory, researchers from CRUK and MedImmune work side by side, with all activities being shared between the partners, from the laboratory set-up, team management, target selection, external communications and projects management. This structure ensures that there is an efficient flow of information to both partners and an equal say in decision-making processes. Importantly, governance is split 50:50 between CRUK and MedImmune with target selection and oversight maintained by three separate committees as follows:

- Target Selection Committee (TSC); reviews target notices (notification of an intent to submit a proposal) and Target Proposals submitted by PIs and makes recommendations on approval of projects. Includes two CRUK academic investigators with a track record in biological research and discovery.
- Joint Management Committee – reviews and approves project work plans, all other outside collaborations, oversees CMAL activities, identifies and reviews arising inventions and approves publication strategy.
- Joint Steering Committee – Sets strategic priorities, resolves conflicts, makes major decisions and can terminate CMAL projects.

To date, the CMAL team has reviewed 56 target notices from ~25 institutes across the U.K. and Europe which has led to 28 Target Proposals being submitted to their TSC for review. Five projects have been accepted into the CMAL with the most advanced on track to deliver in vivo proof of concept in Q4 2017.

It is anticipated that this unique collaboration between CRUK and MedImmune will continue to go from strength to strength and deliver on the partners' shared ambition of collaborative novel antibody discovery for the benefit of cancer patients.

New Paradigms for Dementia Research and the Alzheimer's Research UK Drug Discovery Alliance

Dr. John Davis, Chief Scientific Officer of the Oxford Drug Discovery Institute (ODDI) reviewed the mission, objectives and research processes of the Alzheimer's Research UK's initiatives to accelerate early drug discovery. He noted that the cost of bringing a drug to market has been increasing steadily and is a particularly risky business proposition, especially for the neuroscience therapeutic area which has one of the highest failure rates. Consequently, traditional large pharma companies have been withdrawing from in-house discovery research for CNS disorders, seeking instead new approaches for obtaining target validation and the de-risking that is required before launching a major lead optimization program.

Alzheimer's Research UK is funding a number of drug discovery initiatives as a part of its 'Defeat Dementia' campaign, aiming to inject GBP 100M of charity funding over

Table I. *Expertise and resources provided by each of the Cancer Research UK–MedImmune Alliance Laboratory (CMAL) partners.*

MedImmune	Cancer Research UK
Biologics drug discovery expertise	Novel target ideas from PIs
Staff training and know-how	Unprecedented network of PIs with biology and oncology expertise
Phage libraries (over 100 billion antibodies) and other antibody platforms	Project funding through discovery phase
Project-specific funding for PIs	Operational funding and staff
Capability to commercialize projects	Capability to commercialize projects

PIs, principal investigators.

a period of 5 years, while simultaneously leveraging input from pharma and government. Three of the efforts represent distinct paradigms for promoting early drug discovery: i) the Dementia Consortium, that provides a mechanism for initiating drug discovery from academic projects using an extramural consortium; ii) the Dementia Discovery Fund, a venture capital-like fund to support seed and spin-out ventures; and iii) the Drug Discovery Alliance (DDA) that supports intramural drug discovery resources to facilitate translation to early drug discovery.

Each of these models can be hypothesized to meet differing needs effectively. Common to all is the goal of crossing the 'valley of death' (between target identification and proof of principle) and bring forward novel therapeutic approaches to a point from which pharma funding can be attracted for continued development.

The DDA is comprised of three institutes based in the universities of Oxford, Cambridge and University College London. The institutes are embedded within the host institutions, bringing experienced drug discovery scientists into close proximity with leading CNS academic science. The DDA is positioned uniquely at the nexus of the best of U.K. academic research, several academic 'platform' organizations and with access to multiple pharma and biotech companies as potential development partners.

The DDA has a very flexible remit and is not restricted in its R&D programs. Projects can start from an academic innovation, be nurtured within the DDA and then offered for adoption by interested pharma partners. This combination of the DDA with its Alzheimer's Research UK funding can unlock the best of academic science which might otherwise falter though funding or staffing limitations.

Equally, targets of interest to pharma partners can be developed by the DDA, leavened with appropriate technology or insight from the academic network and ultimately taken forward by the pharma partner.

In an example of the ODDI's work, Dr. Davis described its development of a ubiquitylation platform starting from the identification and synthesis of several tool compounds and concomitant development of assays to verify the efficacy of those compounds. Completing this work package was demonstration of target engagement. This package is then made available to the academic network for further profiling studies, starting points for additional screening for novel compound classes and preparation of leads for in vivo proof of concept.

The IMI European Lead Factory: "A Successful and Innovative Model for Accelerating Early Drug Discovery"

Dr. Phil Jones described the innovative aspects of the discovery model employed by the European Lead Factory (ELF), some of the validated hit series that have emerged and how this model is influencing the European drug discovery ecosystem.

The Innovative Medicines Initiative (IMI) ELF is a major European project established to promote open innovation by generating new lead structures for drug discovery projects in both private and public sectors. A Joint European Compound Library has been established by combining 300,000 compounds from participating pharma companies, supplemented with 200,000 designed and synthesized specifically for the purpose based on scaffold ideas generated by academics, institutions and SMEs from around Europe. The ELF was reported to be on track to achieve its compound objectives by the formal end of the project early in 2018.

Screening of the library and follow-up of the resultant hits is carried out at the European Screening Centre based in Scotland and the Netherlands using advanced robotics for compound logistics and ultra-high-throughput screening (uHTS) in a data-environment that supports protection of IP. From 149 target proposals across Europe received to date, 85 have been accepted. Of those, assays were developed for 59 programs and so far, 56 have been through uHTS in Oss, the Netherlands.

Expert triaging and further characterization of hits, including medicinal chemistry, are available to public programs (academic- and SME-based). The output is one or more high-quality validated hit series that represent excellent starting point(s) for drug discovery or as tools for investigating and validating novel pharmacological approaches with the ultimate aim of creating benefits for patients. From the 56 screens, 44 qualified hit lists resulted from the triaging process and of these 18 improved hit lists (IHL) emerged through the process of repeat assay/sample resynthesis/mechanism of action (MoA) study, target engagement/SAR-based analogue design & synthesis and further screening.

Twelve of these IHLs are currently under further development by the sponsoring investigator, and cover a wide range of target classes (kinase, receptors including GPCR, PPI and several enzyme targets). Three notable successes were described:

- Subnanomolar inhibitor series for the NDM-1 lactamase, to treat carbapenem-resistant bacterial infections (Prof. Chris Schofield, University of Oxford);
- Formation of ScandiCure, by GU Ventures and based on the work of Dr. Margit Mahlapuu from a 320K compound ELF screen for a new type 2 diabetes target implicated in metabolic complications;
- Formation of Keapstone Therapeutics, a joint venture, semi-virtual biotech based on the research of Dr. Richard Mead at the University of Sheffield who similarly started with an ELF screen of the KEAP-1/Nrf-2 complex, and funding from the Parkinson's UK medical charity.

As can be seen from these concrete examples, the IMI-backed ELF project is advancing science, creating new companies and exploiting project synergies for future patient benefit. In conclusion, Dr. Jones added that the public–private partnership embodied in the ELF is:

- Engaged with a wider community of scientists;
- Both sharing existing resources and developing new ones;
- Opening access to new expertise for discovery, at both quality and scale;
- Respecting and generating new IP.

Wellcome Trust and Drug Discovery – What Next?

Dr. Ann Mills-Duggan of the Wellcome Trust reviewed some of the past work of Wellcome in the drug discovery space, with particular emphasis on the renowned Seeding Drug Discovery (SDD) scheme, and looked ahead to the Trust's new strategy and objectives.

Wellcome is the second largest charitable foundation in the world and a major funder in the biomedical space. Through its Innovations Division, Wellcome funds translational work across a broad range of medical interventions and therapeutic areas. Under its initiative of improving human health, the SDD scheme was created in 2005 to fund the development of drug-like small molecules as the springboard for further R&D by the biotechnology and pharmaceutical industry in areas of unmet medical need. With initial funding of GBP 91M, and expansion to GBP 201M in 2010, the scheme has funded 64 projects, with 16 still ongoing. Ten of these 64 projects have been partnered further with pharma and venture capital firms and a number have progressed into clinical trials, most notably a successfully completed phase III trial for a new anti-Gram-negative therapeutic.

Wellcome considers the SDD scheme to have been very successful but is now changing the focus of its future investments in order to be more than a gap funder. In particular, Wellcome's Innovations Division is turning its investment attention to the following:

- Transforming new fundamental biomedical science into innovations, by supporting scientists in their translational efforts;
- Supporting the development of substantial flagship projects by prioritizing its existing project portfolio, adding further financial support with the aim of creating significant impact for human healthcare;
- Adding its support to a small number of national and global initiatives or consortia that aim to have lasting impact in healthcare.

The Wellcome innovator award scheme was outlined as an example of the first of these areas, where awards of GBP 500,000 will be made to researchers to support translational work, including clinical development. The scheme will focus preferentially on mental health, neurological disorders and neglected tropical diseases and researchers must demonstrate how their project will enable their innovation to move to the next stage of development. However, project proposals from outside these areas can also be considered.

As an example of building momentum and reform around global healthcare initiatives, Dr. Mills-Duggan described the Trust's involvement in the CARB-X consortium (www.carb-x.org) which seeks to address the alarming dearth of new antibacterials and relevant diagnostics for infections. The CARB-X consortium is making USD 450M available over the next 5 years for the best science globally to tackle these challenges. To date, awards have been made for the development of 10 new therapies and one proof-of-concept diagnostic. As ever, the Trust remains global in outlook, transparent in making and reviewing application calls and dedicated to funding the very best healthcare science.

Panel Discussion

The symposium concluded with an engaging panel discussion between the presenting speakers and the meeting delegates.

While all speakers had mentioned the importance of 'open collaboration' to bring diverse groups of scientists together, the first question invited the panel members to comment on some of the concurrent challenges of the different cultures and different objectives inherent in many partnerships. In response, Thomas Hanke (Evotec) highlighted the importance of gaining an early understanding of what each partner needed from any collaboration and hence trying to ensure that these various objectives were embedded in the collaboration structure from the beginning. Expanding further, Dave Smith (AZ) focused on collaborations at an early stage of drug discovery, where he experienced that project objectives are often more easily aligned between academic and industrial partners. From the academic perspective, John Davis (ARUK DDI) commented on the need to focus on the respective strengths of the different partners, in order to derive the most effective collaborations. Moving on to legal and contractual aspects of collaborations, the panel were then invited to discuss the challenges of contracting and IP ownership and how their respective organizations were working to reduce the barriers to early-stage research partnerships. Most panel members agreed on the need to be much more open on how IP is viewed and shared at an early stage, even recognizing that at certain points there should be no IP assigned to particular assets and technologies. Phil Jones (EU Screening Centre) also discussed how IP and compound ownership was handled within the context of the IMI ELF and how participating partners benefited from their respective contributions to the screening library.

The discussion then moved to an audience question on how we really define 'external innovation' and what proportion of overall R&D is coming from external sources, sparking a lively debate. While it is difficult to really determine what proportion of research activities could be classed as 'external innovation' (less than 10% being mentioned by one panelist), it was clear that different organizations have differing views on this definition. Changing direction, the panelists were then asked to discuss their opinions on the advantage of geographical 'co-location' for effective R&D collaborations, either between participating scientists on a project or between academia, industry and investment groups. Focusing on the CRUK–MedImmune Alliance, Maria Groves (MedImmune) talked about how critical the neutral laboratory co-location of CRUK and MedImmune scientists was to the success of projects, enabling significant synergies and real-time data sharing to be realized, while also allowing access to broader resources in the respective organizations.

Moving onto the funding of collaborations, the panel was asked to comment on whether they thought money was being appropriately targeted within the UK Biomedical Research community and whether there were opportunities to optimize the funding of collaborative drug discovery. In response, Ann Mills-Duggan (Wellcome Trust) talked about how the Seeding Drug Discovery scheme from the Wellcome Trust had been used in the past and how novel funding vehicles, like Innovator Awards and CARB-X, were now being deployed to optimize the funding of drug discovery projects. An engaging panel discussion continued around other topics introduced by the audience, including the need to collaborate around technologies and how to solve the industry-wide challenge of identifying and validating new biological targets for many diseases.

Finally, the panelists were invited to describe their vision for how they would like to see partnerships develop in the future, leaving the audience inspired by what possibilities could exist.

Disclosures

All authors are in paid employment of their respective organizations. All are also SMR committee members, for which no remuneration is paid.

Reference

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